Effects of Controlled-Release Metoprolol on Total Mortality, Hospitalizations, and Well-being in Patients With Heart Failure

The Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF)

Åke Hjalmarson, MD, PhD
Sidney Goldstein, MD
Björn Fagerberg, MD, PhD
Hans Wedel, PhD
Finn Waagstein, MD, PhD
John Kjekshus, MD, PhD
John Wikstrand, MD, PhD
Dia El Allaf, MD
Jirí Vítovec, MD, PhD
Jan Aldershvile, MD, PhD
Matti Halinen, MD, PhD
Rainer Dietz, MD
Karl-Ludwig Neuhaus, MD
András Jánosi, MD, DSc
Gudmundur Thorgeirsson, MD, PhD
Peter H. J. M. Dunselman, MD, PhD
Lars Gullestad, MD
Jerzy Kuch, MD
Johan Herlitz, MD, PhD
Peter Rickenbacher, MD
Stephen Ball, MD, PhD
Stephen Gottlieb, MD
Prakash Deedwania, MD
for the MERIT-HF Study Group

Context Results from recent studies on the effects of β_1-blockade in patients with heart failure demonstrated a 34% reduction in total mortality. However, the effect of β_1-blockade on the frequency of hospitalizations, symptoms, and quality of life in patients with heart failure has not been fully explored.

Objective To examine the effects of the β_1-blocker controlled-release/extended-release metoprolol succinate (metoprolol CR/XL) on mortality, hospitalization, symptoms, and quality of life in patients with heart failure.

Design Randomized, double-blind controlled trial, preceded by a 2-week single-blind placebo run-in period, conducted from February 14, 1997, to October 31, 1998, with a mean follow-up of 1 year.

Setting Three hundred thirteen sites in 14 countries.

Participants Patients (n = 3991) with chronic heart failure, New York Heart Association (NYHA) functional class II to IV, and ejection fraction of 0.40 or less who were stabilized with optimum standard therapy.

Interventions Patients were randomized to metoprolol CR/XL, 25 mg once per day (NYHA class II), or 12.5 mg once per day (NYHA class III or IV), titrated for 6 to 8 weeks up to a target dosage of 200 mg once per day (n = 1990); or matching placebo (n = 2001).

Main Outcome Measures Total mortality or any hospitalization (time to first event), number of hospitalizations for worsening heart failure, and change in NYHA class, by intervention group; quality of life was assessed in a substudy of 741 patients.

Results The incidence of all predefined end points was lower in the metoprolol CR/XL group than in the placebo group, including total mortality or all-cause hospitalizations (the prespecified second primary end point; 641 vs 767 events; risk reduction, 19%; 95% confidence interval [CI], 10%-27%; $P<.001$); total mortality or hospitalizations due to worsening heart failure (311 vs 439 events; risk reduction, 31%; 95% CI, 20%-40%; $P<.001$), number of hospitalizations due to worsening heart failure (317 vs 451; $P<.001$); and number of days in hospital due to worsening heart failure (3401 vs 5303 days; $P<.001$). NYHA functional class, assessed by physicians, and McMaster Overall Treatment Evaluation score, assessed by patients, both improved in the metoprolol CR/XL group compared with the placebo group ($P = .003$ and $P = .009$, respectively).

Conclusions In this study of patients with symptomatic heart failure, metoprolol CR/XL improved survival, reduced the need for hospitalizations due to worsening heart failure, improved NYHA functional class, and had beneficial effects on patient well-being.

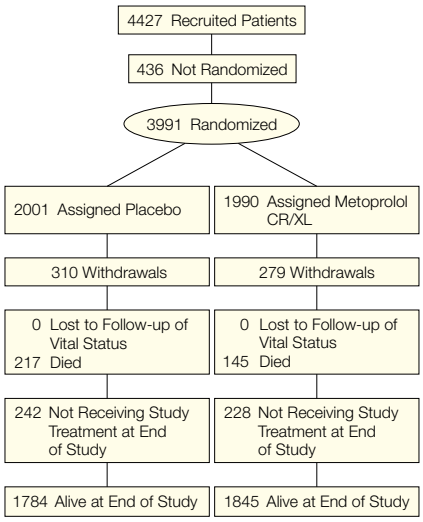
JAMA. 2000;283:1295-1302 www.jama.com

CHRONIC HEART FAILURE IS A common disease that has a poor prognosis and periods of incapacitating symptoms necessitating recurrent hospital admissions.[1,2] The most common modes of death are sudden death or death from worsening heart failure.[3] The discovery of the pathophysiological impor-

For editorial comment see p 1335.

Author Affiliations and Financial Disclosures are listed at the end of this article.
Corresponding Author/Reprints: Björn Fagerberg, MD, PhD, Wallenberg Laboratory for Cardiovascular Research, Sahlgrenska University Hospital, SE-413 45 Gothenburg, Sweden (e-mail: bjorn.fagerberg@medfak.gu.se).

Figure 1. Patient Flow in the Randomized Controlled Trial



CR/XL indicates controlled release/extended release.

tance of neuroendocrine activation in heart failure and the possibility of modifying such mechanisms of the disease process have greatly improved treatment in clinical practice.[4] Thus, angiotensin-converting enzyme (ACE) inhibitors have been established as standard therapy for patients with chronic heart failure due to left ventricular systolic dysfunction, with proven effects on mortality and symptoms related to worsening heart failure.[4,5] Despite the benefits of this mode of therapy, mortality and morbidity remain high for patients with heart failure.

The role of β-blocker treatment in the management of chronic heart failure has taken time to clarify. The results from meta-analyses of previous smaller studies of various β-blockers in heart failure, including the carvedilol studies, have indicated beneficial effects.[6-8] Two studies on the survival effects of β_1-blockade published in 1999, the Cardiac Insufficiency Bisoprolol Study (CIBIS) II[9] and the present Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF),[10] demonstrated that total mortality was reduced by 34%.

Although the survival benefit of β_1-blockade in chronic heart failure due to systolic dysfunction has been established, the need for hospital care, safety aspects, symptom alleviation, and improved quality of life are additional important aspects of treatment, for both the patient and the clinician. However, the impact of β-blockers on these outcomes has not been fully explored. Accordingly, the MERIT-HF was designed to study the effects of controlled-release/extended-release metoprolol succinate (metoprolol CR/XL) on mortality, as previously reported,[10] as well as hospitalizations, symptoms, and quality of life.

METHODS

Organization

The MERIT-HF was a randomized, double-blind placebo-controlled trial with a single-blind, 2-week placebo run-in period. Randomization was performed according to an optimal allocation procedure, which balanced the metoprolol CR/XL and placebo groups for investigational site, age, sex, race/ethnicity, cause of heart failure, previous acute myocardial infarction (AMI), and, within the previous AMI group, time since last AMI, diabetes mellitus, ejection fraction, and New York Heart Association (NYHA) functional class. An interactive voice recording system (Covance, Princeton, NJ) was used to provide investigators with the computer-generated study drug number based on the optimal allocation procedure.

A total of 3991 patients with symptomatic chronic heart failure and decreased ejection fraction who were stabilized with standard treatment were randomized (FIGURE 1) at 313 investigational sites in the United States and 13 European countries (Belgium, Czech Republic, Denmark, Finland, Germany, Hungary, Iceland, the Netherlands, Norway, Poland, Sweden, Switzerland, and the United Kingdom). The study was approved by the institutional review board of each hospital and all patients provided written informed consent.

The Independent Endpoint Committee, whose 5 members were unaware of treatment status, classified all events from copies of medical charts and other documents according to prespecified definitions. An Independent Safety Committee monitored safety issues during the study. The stopping rule for efficacy was based on the total number of expected deaths, analyzed based on the intent-to-treat principle. The study used an asymmetrical group sequential procedure to monitor total mortality. A Peto-type boundary[11] was used for monitoring a positive trend. This approach favors a large critical Z-value for all interim tests before the end of the trial. The cumulative α level was planned to be .0012, .0024, and .0036 at the first, second, and third interim analyses to take place when 25%, 50%, and 75%, respectively, of the total number of expected deaths had occurred. The cumulative probability of early stopping for harm was planned to be .005, .010, and .015 at the first, second, and third interim analyses, respectively.

Outcome Measures

There were 2 primary outcome measures: total mortality and the combined end point of total mortality or all-cause hospitalization (time to first event). The MERIT-HF was stopped early, on October 31, 1998, because the second preplanned interim analysis showed a significant 34% reduction in total mortality in the metoprolol CR/XL group.[10] As previously reported, 145 patients died in the metoprolol CR/XL group compared with 217 in the placebo group.[10]

The following combined end points (time to first event) were also predefined: total mortality or hospitalization due to worsening heart failure; death or heart transplantation; cardiac death or nonfatal AMI; and total mortality or hospitalization due to worsening heart failure or emergency department visit due to worsening heart failure. Other end points were number of hospitalizations due to heart failure and other cardiovascular causes, withdrawal of study drug due to worsening heart failure, and change in NYHA functional class. Effect on quality of life was assessed in a substudy that was conducted in the United States, United Kingdom, Sweden, Norway, and the Netherlands.

Patients

The major inclusion criteria were symptomatic heart failure for at least 3 months,

corresponding to NYHA class II to IV, and a left ventricular ejection fraction of 0.40 or less in men and women aged 40 to 80 years. For patients with an ejection fraction between 0.36 and 0.40, it was mandatory that a 6-minute walk test result did not exceed 500 yd (450 m). Resting heart rate had to be 68/min or more. Patients had to be receiving optimal treatment (defined as any combination of diuretics and an ACE inhibitor) for at least 2 weeks prior to randomization. If an ACE inhibitor was not tolerated, hydralazine, long-acting nitrate, or an angiotensin II blocker could be used. Digitalis also could be prescribed. In addition, the inclusion criteria included a stable clinical condition during the 2-week placebo run-in phase before randomization (TABLE 1).

The main exclusion criteria included AMI or unstable angina pectoris within 28 days before randomization, indication or contraindication for treatment with β_1-blockade, severe decompensated heart failure (eg, pulmonary edema, hypoperfusion), or supine systolic blood pressure of less than 100 mm Hg. A more detailed description of the study protocol has been published previously.[12]

Treatment and Measurements

At the randomization visit, patients were allocated to treatment with metoprolol CR/XL or placebo administered once daily. The starting dosage was one 25-mg tablet once per day (half of a 25-mg tablet was recommended for patients with NYHA functional class III or IV). It was recommended to double the dosage after each 2-week period to reach the target dosage level of 200 mg/d of metoprolol CR/XL or placebo. This regimen could be modified according to the judgment of the investigator. If a patient did not tolerate increased titration of study drug, temporary reduction in dosage or increase in diuretic dosage was advocated. During follow-up, patient visits were scheduled every third month.

At each visit, the investigators judged and documented the patient's NYHA functional class. The Minnesota Living with Heart Failure questionnaire was completed by patients at randomization, after each 6-month treatment period, and at study closure.[13] This questionnaire consists of 21 items; the total score ranges from 0 to 105, with lower scores indicating better quality of life. The McMaster Overall Treatment Evaluation questionnaire (OTE) was completed by the patients after each 6-month treatment period and at study closure.[14] This questionnaire has 3 items that assess the overall effect according to whether a patient experienced any change in activity limitation, symptoms, or feelings since the treatment started, using 7-point scales. Any improvement or deterioration was subsequently scored by the patient in terms of magnitude and importance to the patient's ability to carry out daily activities.

Hospitalizations were defined as care at an acute-care hospital lasting for 24 hours or more and had to be separated from other hospitalizations by separate dates for discharge and admission. Transfer from one ward to a different type of hospital ward was counted as 1 hospitalization. Hospitalization due to heart failure was defined as documentation in the medical charts indicating worsening heart failure as the reason for hospitalization. If competing reasons were judged to be of equal importance, the heart failure diagnosis took preference. Emergency department visit was defined as care in an urgent fashion with urgent-care treatment such as intravenous medication.

Statistical Analyses

The power calculation showed that the mean follow-up time had to be 2.4 years if 1600 patients were randomized to each treatment group over 14 months. This was based on a significance level of $\alpha = .04$ (2-sided) for the first primary end point of total mortality and $\alpha = .01$ for the second primary end point of total mortality or any hospitalization (time to first event), a power of at least 80% ($\beta \leq .2$), and the following assumptions: a 9.4% mean annual mortality in the placebo group, a mean risk-reducing effect of metoprolol CR/XL of 30% (with treatment), and a withdrawal rate from study drug of 20% the first year and 5% annually thereafter.[12] Because patient recruitment proceeded faster than planned, 3991 patients were randomized during the recruitment period, thereby increasing the power of the study.

Table 1. Baseline Characteristics of the Randomization Groups*

Characteristics	Treatment Group: Metoprolol CR/XL (n = 1990)	Treatment Group: Placebo (n = 2001)
Age, mean, y	63.9	63.7
Sex, % female	23	22
White, %	94	94
Ischemic etiology of heart failure, %	65	66
NYHA class, %		
II	41	41
III	56	55
IV	3.4	3.8
Ejection fraction, mean	0.28	0.28
Previous myocardial infarction, %	48	49
Time since last myocardial infarction <1 y, %	8	7
Hypertension, %	44	44
Diabetes mellitus, %	25	24
Medications, %		
Diuretics	91	90
ACE inhibitor	89	90
A-II–blocker	7	6
ACE inhibitor or A-II–blocker	95	96
Digitalis	63	64
Spironolactone	7	8

*CR/XL indicates controlled release/extended release; NYHA, New York Heart Association; ACE, angiotensin-converting enzyme; and A-II, angiotensin II.

The analysis was by intent to treat. The main analyses used the log-rank test for the comparison of the 2 randomized groups and the Cox proportional hazards model to calculate relative risk and 95% confidence intervals (CIs). Additional Cox proportional hazards regression analyses of the combined end points of total mortality or all-cause hospitalizations (time to first event) and total mortality or hospitalizations due to heart failure (time to first event) were performed to explore any unfavorable outcome in prespecified risk groups, defined by entry characteristics as previously described.[10,12] For ejection fraction, systolic and diastolic blood pressure, and heart rate, patients in the lowest tertile were compared with those in the middle and upper tertiles. Regarding age, the upper tertile was compared with the middle and lower tertiles. New York Heart Association class, etiology of heart failure, smok-

ing status, sex, previous AMI, diabetes mellitus, and hypertension were also prespecified as risk groups. Ischemic and nonischemic heart disease have been defined as the 2 major causes of heart failure. Hypertension was defined as pharmacologically treated high blood pressure, and diabetes mellitus was defined as a clinical diagnosis made by the investigator. More than 180 events in any such subgroup would yield a power of at least 70% to detect a 30% increase in risk. Data on complementary subgroups having less than 180 events have also been depicted.

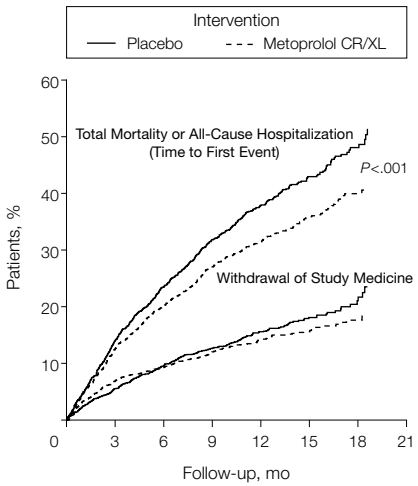
The sample size calculation for the quality of life substudy showed that with 419 patients in each group, it would be possible to detect a difference of 3 units on total Living with Heart Failure score between the treatment groups based on the following assumptions: SD for change = 16, $\alpha = .05$, and $\beta = .20$. A net difference of 3 units was judged to be a clinically meaningful change. The changes in NYHA class and OTE score were tested by means of a permutation test using raw data scores. Changes in Living with Heart Failure score were analyzed using an analysis of covariance model with adjustment for the baseline Living with Heart Failure score. A 2-sided $P<.05$ was regarded as statistically significant.

RESULTS

Randomization began on February 14, 1997, and the last patient was randomized on April 14, 1998. The International Steering Committee stopped the study on October 31, 1998, on recommendation from the Independent Safety Committee. The second preplanned interim analysis (at the halfway point) had shown that the predefined criterion for termination of the study was met and exceeded. In total, 2004 patient-years were accumulated in the metoprolol CR/XL group and 1977 in the placebo group (total mortality). The corresponding patient-years for the combined end point of total mortality or all-cause hospitalization were 1650 vs 1600 patient-years, and for total mortality or hospitalization for worsening heart failure were 1880 vs 1840 patient-years, respectively. The mean follow-up time was 1 year.

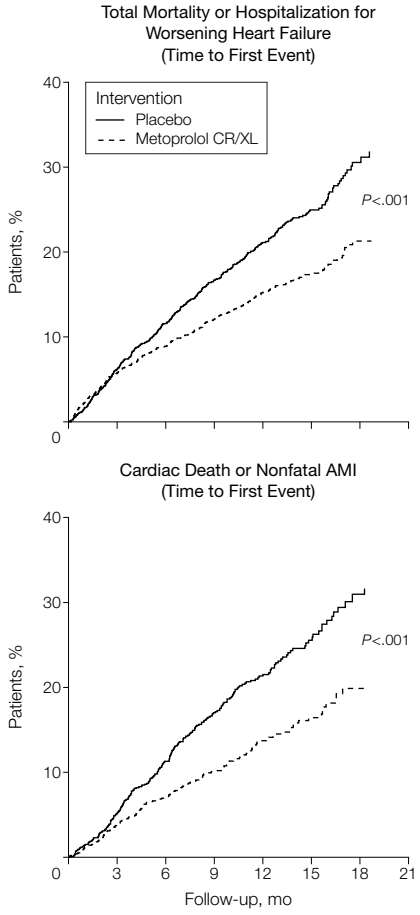
The 2 groups were similar at entry (Table 1). Furosemide daily dosage at baseline and during follow-up was 66 mg/d and 70 mg/d in the metoprolol CR/XL group and 65 mg/d and 73 mg/d in the placebo group, respectively. The ACE inhibitor daily dosage was also similar at baseline and during follow-up in both randomization groups. For enalapril, it was 14 mg/d at baseline and 15 mg/d at follow-up in both groups; corresponding dosages at baseline and follow-up, respectively, for cap-

Figure 2. Cumulative Percentages (Time to First Event) for the Combined End Point of Total Mortality or All-Cause Hospitalization



Cumulative (all-cause) withdrawal of study drug has also been illustrated, including 310 patients in the placebo group and 279 in the controlled-release/extended-release metoprolol (metoprolol CR/XL) group.

Figure 3. Cumulative Percentages (Time to First Event) for Total Mortality or Hospitalization for Worsening Heart Failure and Cardiac Death or Nonfatal Acute Myocardial Infarction (AMI)



CR/XL indicates controlled release/extended release.

Table 2. Effect of Metoprolol CR/XL and Placebo on Combined End Points*

Combined End Points	Metoprolol CR/XL Group, No. of Patients (n = 1990)	Placebo Group, No. of Patients (n = 2001)	Total	Risk Reduction, % (95% Confidence Interval)
Total mortality or all-cause hospitalization	641	767	**1408**	19 (10-27)
Total mortality or hospitalization due to worsening heart failure	311	439	**750**	31 (20-40)
Death or heart transplantation	150	218	**368**	32 (16-45)
Cardiac death or nonfatal acute myocardial infarction	139	225	**364**	39 (25-51)
Total mortality or hospitalization or emergency department visit due to worsening heart failure	318	455	**773**	32 (21-41)

*Only the first end point that occurred in each patient was counted. $P<.001$ for all comparisons. CR/XL indicates controlled release/extended release.

topril were 68 mg/d vs 70 mg/d in the metoprolol CR/XL group and 60 mg/d vs 64 mg/d in the placebo group, and for lisinopril were 17 mg/d vs 17 mg/d in the metoprolol CR/XL group and 16 mg/d vs 16 mg/d in the placebo group.

The patients who participated in the quality of life substudy (n = 741) had characteristics similar to those of the entire group (mean age, 64.4 years; female sex, 28%; NYHA class II, 39%; NYHA class III, 56%; NYHA class IV, 5%; mean ejection fraction, 0.27; previous AMI, 51%; and treatment with ACE inhibitor or angiotensin II blocker, 96%).

Combined End Points

Metoprolol CR/XL significantly reduced all combined end points (time to first event) compared with placebo (TABLE 2, FIGURE 2, and FIGURE 3). Total mortality or all-cause hospitalizations (the prespecified second primary end point) was reduced by 19% (Figure 2), total mortality or hospitalization for worsening heart failure by 31% (Figure 3), death or heart transplantation by 32%, cardiac death or nonfatal AMI by 39% (Figure 3), and total mortality or hospitalization due to worsening heart failure or emergency department visit due to worsening heart failure by 32%. No significant increase in total mortality or all-cause hospitalizations (time to first event) or in total mortality or hospitalizations due to worsening heart failure (time to first event) were observed in any of the predefined subgroups analyzed for safety reasons (FIGURE 4).

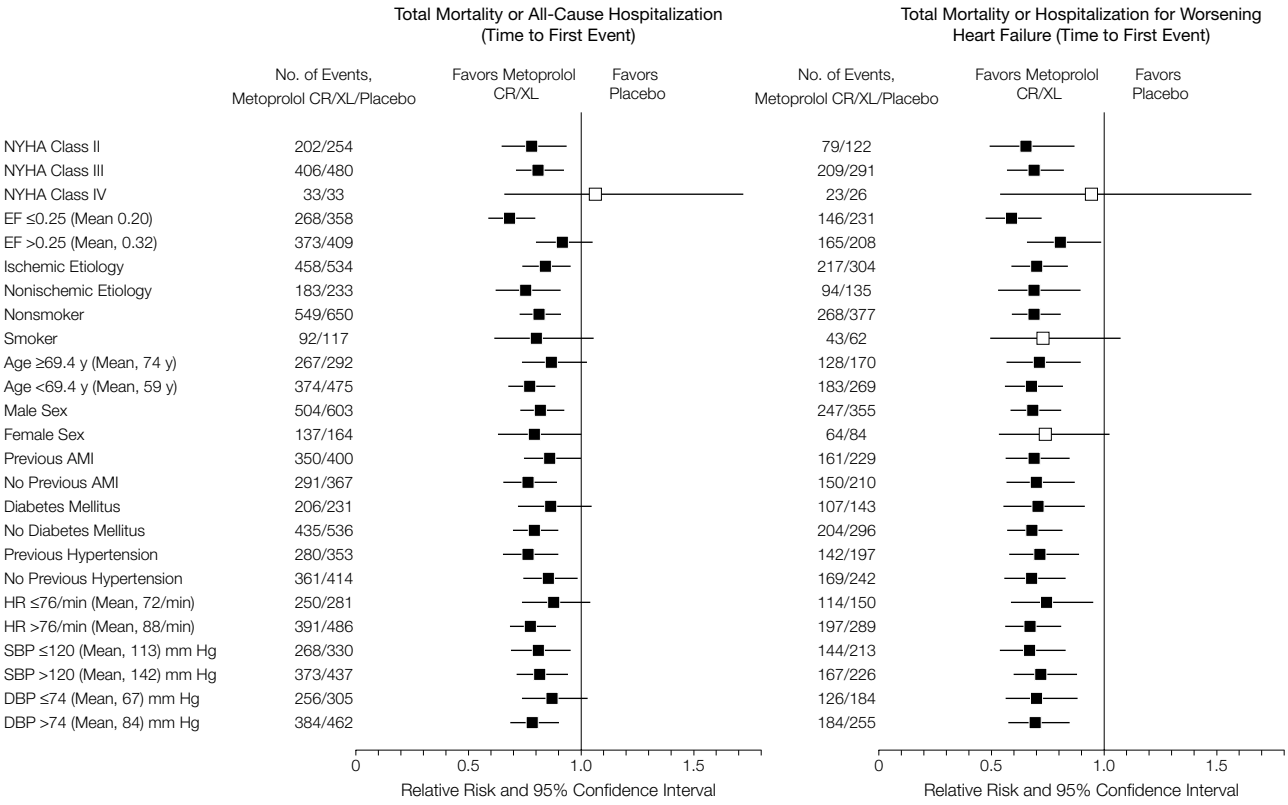
Hospitalizations

Compared with placebo, metoprolol CR/XL reduced the number of patients with any hospitalization, the total number of hospitalizations, and the total number of days in the hospital due to all causes (FIGURE 5, TABLE 3). This was mainly explained by a reduction in the number of patients who were hospitalized for worsening heart failure, accompanied by decreases in the total number of hospitalizations and total number of days in the hospital due to heart failure (Table 3, Figure 5). To account for the improved survival with metoprolol CR/XL, the proportion of days spent alive outside the hospital was also calculated as 95% in the metoprolol CR/XL group and 93% in the placebo group ($P<.001$).

Physician and Patient Assessment of Treatment Effects

Physicians classified NYHA functional class at baseline and at the last visit in

Figure 4. Absolute Numbers and Relative Risks (Time to First Event) for Total Mortality or All-Cause Hospitalization and for Total Mortality or Hospitalization Due to Worsening Heart Failure in Predefined Subgroups According to Baseline Characteristics



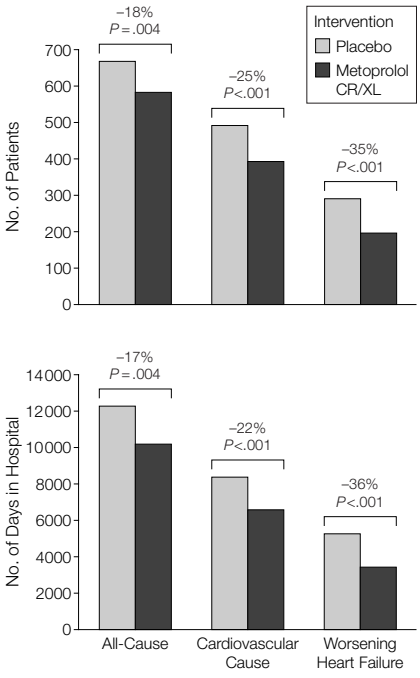
Filled squares indicate subgroups with a total of 180 events or more; open squares, subgroups with a total of less than 180 events (low power); CR/XL, controlled release/extended release; NYHA, New York Heart Association; EF, ejection fraction; AMI, acute myocardial infarction; HR, heart rate; SBP, systolic blood pressure; and DBP, diastolic blood pressure.

the study. Improvement was recorded in 28.6% vs 25.8% of the metoprolol CR/XL and placebo groups, respectively (26.0% vs 24.3% improved 1 class; 2.6% vs 1.5% improved 2 classes); 65.4% vs 66.7% were unchanged; 6.0% vs 7.5% deteriorated (5.7% vs 6.8% deteriorated 1 class, 0.3% vs 0.7% deteriorated 2 classes). These data show a more favorable change in NYHA class in the metoprolol CR/XL group compared with the placebo group ($P = .003$).

There was a statistically significant improvement in the OTE score in the metoprolol CR/XL group compared with placebo ($P = .009$; FIGURE 6). In the metoprolol CR/XL group, 185 patients (50%) reported improvement, and patients' evaluations of the importance of this change were available for 184 patients, showing that 132 patients (72%) judged this improvement as important, very important, or extremely important to carry out daily activities. In the placebo group, 148 patients (40%) reported improvement that was judged to be important, very important, or extremely important by 72% of these patients.

Living with Heart Failure forms completed at randomization and at the last visit were available for 670 patients. Scores were similar at randomization in the 2 study groups. The total Living with Heart Failure score, adjusted for the score at baseline, decreased (improved) by 0.7 in the metoprolol CR/XL group (n = 331)and increased (deteriorated) by 0.2 in the placebo group (n = 339) (mean difference, –0.9; 95% CI, –3.4 to 1.6; $P = .20$).

Figure 5. Number of Patients Hospitalized and Total Number of Days Spent in the Hospital Due to Any Cause, Cardiovascular Cause, or Worsening Heart Failure



CR/XL indicates controlled release/extended release. Relative differences between the groups are given in percentages.

Withdrawal of Study Drug

The most frequent adverse events necessitating withdrawal of study drug were worsening heart failure, atrial fibrillation, and angina pectoris, and these events were less frequent in the metoprolol CR/XL group than in the placebo group (TABLE 4). Dizziness, bradycardia, and hypotension occurred slightly more frequently in the metoprolol CR/XL group.

Permanent withdrawal of study drug due to any cause during the study is shown in Figure 2 and occurred in 279 patients in the metoprolol CR/XL group and 310 patients in the placebo group (risk reduction for withdrawal decreased by 10% in the metoprolol CR/XL group; 95% CI, –5% to 24%; $P = .18$). Permanent withdrawal of study drug due to any adverse event occurred in 196 patients in the metoprolol CR/XL group and 234 patients in the placebo group (risk reduction, 17%; 95% CI, –1% to 31%; $P = .06$). Worsening heart failure was the main reason for withdrawal in 64 patients (3.2%) in the metoprolol CR/XL group and 85 (4.2%) in the placebo group (risk reduction, 25%; 95% CI, –4% to 46%; $P = .08$).

COMMENT

This study demonstrated that metoprolol CR/XL, a β_1-blocker given once per day in addition to conventional therapy to patients with chronic heart failure, improved survival as previously reported,[10] reduced the need for hospital admissions due to worsening heart failure, and improved symptoms and well-being.

In the MERIT-HF, there were no differences between the study groups in underlying pharmacological treatment for heart failure at baseline or during follow-up. All-cause mortality or hospitalizations (the prespecified second primary end point, time to first event) was significantly reduced by 19% in the metoprolol CR/XL group. Correspondingly, total deaths or hospitalizations due to worsening heart failure were reduced by 31%. The annual mortality in the placebo group was 11.2% and total mortality was reduced by 34% in the metoprolol CR/XL group.[10] Despite this improved survival and more patients at risk for hospital admissions, fewer patients were hospitalized due to any cause

Table 3. Cause-Specific Data for Number of Patients Hospitalized at Least Once, Total Number of Hospitalizations, and Total Number of Days Spent in the Hospital

Hospitalizations	Metoprolol CR/XL (n = 1990)	Placebo (n = 2001)	*P* Value
Due to all causes			
Patients with any hospitalization (%)	581 (29.1)	668 (33.3)	.004
Hospitalizations	1021	1149	.005
Days in hospital	10 172	12 262	.004
Due to cardiovascular causes			
Patients with any hospitalization (%)	394 (19.8)	494 (24.7)	<.001
Hospitalizations	649	773	<.001
Days in hospital	6584	8403	<.001
Due to worsening heart failure			
Patients with any hospitalization (%)	200 (10.0)	294 (14.7)	<.001
Hospitalizations	317	451	<.001
Days in hospital	3401	5303	<.001

*CR/XL indicates controlled release/extended release.

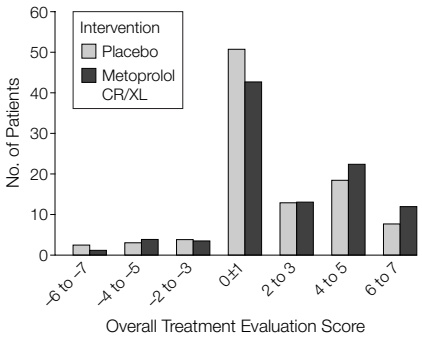
in the metoprolol CR/XL group, mainly due to a 35% reduction in the number of patients hospitalized for worsening heart failure. The total number of days in the hospital due to heart failure was reduced to a similar degree in the metoprolol CR/XL group, with no increase in hospitalizations for other reasons. Conversely, the number of days alive without need for hospital care was higher in the metoprolol CR/XL group than in the placebo group. Given the comparatively low cost of β-blocker therapy and the high cost of hospitalizations, the 36% reduction in days spent in the hospital for worsening heart failure suggests a positive effect on health care costs with metoprolol CR/XL treatment in patients with chronic heart failure. It is noteworthy that there was considerable comorbidity among these patients because hospitalizations due to noncardiovascular causes accounted for 30% of all days spent in the hospital and one quarter of all days was due to cardiovascular causes other than worsening heart failure (Table 3, placebo group).

Our results are consistent with data from the CIBIS-II study, in which treatment with the β_1-blocker bisoprolol also reduced hospital admissions due to any cause and due to worsening heart failure.[9] The smaller carvedilol studies also have shown reductions in hospitalizations.[7,8]

The mechanisms involved in the beneficial effects of β_1-blockade in patients with chronic heart failure are not completely known. However, it is well established that in patients with chronic heart failure due to systolic dysfunction of various etiologies, metoprolol has favorable effects on left ventricular geometry and function, myocardial energy balance, and exercise capacity.[15-17] In patients with dilated cardiomyopathy, metoprolol has been found to reduce heart transplantations and to improve NYHA functional class and quality of life.[17,18] In line with these previous observations, the MERIT-HF results showed that symptoms of heart failure improved according to judgments made by the responsible physicians, as did quality of life as assessed by patients on the OTE. Improvement in quality of life was of considerable importance for a large proportion of patients. The observation that the OTE but not the Living with Heart Failure questionnaire showed significant improvement in quality of life may reflect the different constructions of these 2 instruments. The former is a global assessment of treatment effects on activity limitation, symptoms, and feelings, whereas the latter is a 21-item questionnaire used at baseline and during follow-up (see "Methods" section). Given the decrease in hospitalizations and the improvement in both NYHA class and in OTE score, the sensitivity of the Living with Heart Failure questionnaire to assess beneficial changes in quality of life might be questionable. A recent study showed that retrospective measures, such as the 7-point scale used in the OTE, may be more sensitive to change than serial measures and also correlate more strongly with patient's' satisfaction with change.[19] The previously published documentation of the effect of β-blockade on the Living with Heart Failure score in patients with heart failure relates mainly to nonselective β-blockade with carvedilol therapy, showing no statistically significant effect.[20-22]

Metoprolol CR/XL was well tolerated. Withdrawal of study drug from all causes was 10% lower[10] and withdrawal due to worsening heart failure was 25% lower in the metoprolol CR/XL group compared with the placebo group. These findings are of interest, especially against the background that no metoprolol CR/XL test dose had been given prior to initiating double-blind treatment. For the most frequent adverse reactions leading to withdrawal of study drug, including worsening heart failure, atrial fibrillation, and angina pectoris, withdrawal was more common in the placebo group. Fewer than 1 of 100 patients treated for 1 year

Figure 6. Overall Treatment Evaluation Score as Judged by Patients at the End of the Study



CR/XL indicates controlled release/extended release. Zero indicates no change; – 7, maximum deterioration; and 7, maximum improvement. A significant (P = .009) improvement was observed in the metoprolol CR/XL group vs the placebo group.

Table 4. Cause-Specific Adverse Events Leading to Withdrawal of Study Drug According to Absolute Value for Net Difference Between the Randomization Groups*

Adverse Events†	Metoprolol CR/XL, No. (%)	Placebo, No. (%)	Net Difference, % per First Year
Heart failure	78 (3.9)	117 (5.8)	–2.2
Atrial fibrillation	2 (0.1)	17 (0.8)	–0.8
Angina pectoris	9 (0.5)	20 (1.0)	–0.6
Bradycardia‡	16 (0.8)	5 (0.2)	0.6
Hypotension‡	12 (0.6)	5 (0.2)	0.4
Dizziness‡	12 (0.6)	6 (0.3)	0.3
Fatigue	14 (0.7)	9 (0.4)	0.3
Dyspnea	15 (0.8)	12 (0.6)	0.2
Myocardial infarction§	11 (0.6)	15 (0.7)	–0.2
All patients with any adverse event	196 (9.8)	234 (11.7)	–2.2

*CR/XL indicates controlled release/extended release. Adverse events that led to withdrawal of study drug are specified if the frequency of the cause-specific adverse event was greater than 0.5% in either group. The net difference (metoprolol CR/XL – placebo) refers to the percentage of patients treated during the first year of treatment (1836 vs 1819 patient-years of follow-up until withdrawal of study medicine or death in the metoprolol CR/XL group and placebo group, respectively).
†Patients may have had more than 1 reason for withdrawal.
‡The cumulative net difference for bradycardia, dizziness, and hypotension in the metoprolol CR/XL group was 0.9%.
§The total number of patients who had a myocardial infarction during follow-up was 35 vs 41 in the metoprolol CR/XL and placebo groups, respectively.

withdrew from metoprolol CR/XL treatment because of bradycardia, dizziness, or hypotension. There were no specific safety concerns observed in any of the preidentified risk groups.

In this study, controlled-release/extended-release metoprolol succinate, once per day, was used. This formulation leads to a more pronounced and even β-blockade over 24 hours compared with conventional immediate-release metoprolol tartrate tablets, 50 mg 3 times per day.[23] In patients with chronic heart failure, the dosing schedule can be simplified with metoprolol CR/XL and the target dosage also can be increased to 200 mg once per day compared with 50 mg 3 times per day with the conventional formulation, without increasing the peak plasma concentration of the drug.[24] The titration schedule started with a low once-daily dosage, 25 mg/d for those in NYHA class II and 12.5 mg/d for those in NYHA class III or IV, with increased titration every 2 weeks. The target dosage, 200 mg/d, was reached by 64% of the patients, and 87% received 100 mg/d or more.[10] The mean dosage was 159 mg/d.[10] The combined results from MERIT-HF and CIBIS II demonstrate that it is safe to treat patients with heart failure with β_1-blockers by using a low starting dosage and gradual increased titration.

This study has several limitations. Several categories of patients were not included (eg, patients with severe heart failure who were confined to bed, patients with heart failure and an ejection fraction of more than 0.40, and patients with heart failure early after AMI). The group of patients in NYHA functional class IV was small, resulting in wide 95% CIs overlapping those in NYHA functional classes II and III.[10] However, results from a recent meta-analysis of several studies indicate that treatment with β-blockers confers significant beneficial effects on the clinical outcome in patients in NYHA class IV.[25]

In conclusion, the MERIT-HF study demonstrates that treatment with metoprolol CR/XL once daily added to standard therapy for patients with mild to severe heart failure due to left ventricular systolic dysfunction improves survival, reduces the need for hospital admissions due to worsening heart failure, improves symptoms of heart failure, and increases well-being.

Author Affiliations: Department of Cardiology (Drs Hjalmarson, Waagstein, and Herlitz) and Wallenberg Laboratory for Cardiovascular Research (Drs Fagerberg and Wikstrand), Sahlgrenska University Hospital, and the Nordic School of Public Health (Dr Wedel), Göteborg, Sweden; Henry Ford Hospital, Detroit, Mich (Dr Goldstein); Department of Medicine, Rikshospitalet, Oslo, Norway (Drs Kjekshus); Baerums Sykehus, Baerum, Norway (Dr Gullestad); Service de Cardiologie et de Réanimation Cardiaque, Centre Hospitalier Hutois, Huy, Belgium (Dr El Allaf); 2 Interní Klinika, Fakultní Nemocnice, Brno, Czech Republic (Dr Vítovec); Department of Medicine B, Rigshospitalet, Copenhagen, Denmark (Dr Aldershvile); Accident and Emergency Department, Kuopio University Hospital, Kuopio, Finland (Dr Halinen); Franz-Volhard Klinik, Charité Campus, Berlin-Buch, Germany (Dr Dietz); Klinikum-Kassel, Medizinische Klinik II, Kassel, Germany (Dr Neuhaus); Szent János Hospital, Budapest, Hungary (Dr Jánosi); Department of Medicine, Landspítalinn, University Hospital, Reykjavík, Iceland (Dr Thorgeirsson); Department of Cardiology, St Ignatius Ziekenhuis, Breda, the Netherlands (Dr Dunselman); Department of Cardiology, Warsaw School of Medicine, Warsaw, Poland (Dr Kuch); Kardiologie, Kantonsspital Bruderholz, Bruderholz, Switzerland (Dr Rickenbacher); Institute for Cardiovascular Research, Leeds General Infirmary, Leeds, England (Dr Ball); Division of Cardiology, University of Maryland, Baltimore (Dr Gottlieb); and the Department of Veterans Affairs Medical Center, Fresno, Calif (Dr Deedwania).

Independent Safety Committee: Desmond G. Julian, England; David L. DeMets, Kanu Chatterjee, Jan Feyzi, United States.

Independent Endpoint Committee: Seppo Lehto, Finland; Pal Kárpáti, Hungary; Wolfgang Motz, Germany; Ola Samuelsson, Sweden; Jan Willem Viersma, the Netherlands.

Financial Disclosures: Dr Fagerberg has received an honorarium from AstraZeneca, the sponsor of the study, as secretary for the International Executive and Steering committees of the MERIT-HF; Dr Wedel has received an honorarium from AstraZeneca as statistician for the study; and Dr Wikstrand is senior medical advisor at AstraZeneca.

MERIT-MF Study Group: A complete list of the members of the MERIT-HF Study Group was published previously (*Lancet*. 1999;353:2001-2007).

Funding/Support: This study was supported by grants from AstraZeneca.

REFERENCES

1. Senni M, Tribouilloy CM, Rodeheffer RJ, et al. Congestive heart failure in the community: trends in incidence and survival in a 10-year period. *Arch Intern Med*. 1999;159:29-34.

2. Krumholz HM, Parent EM, Tu N, et al. Readmission after hospitalization for congestive heart failure among Medicare beneficiaries. *Arch Intern Med*. 1997; 157:99-104.

3. Narang R, Cleland JGF, Erhardt L, et al. Mode of death in chronic heart failure: a request and proposition for more accurate classification. *Eur Heart J*. 1996; 17:1390-1403.

4. Steering Committee and Membership of the Advisory Council to Improve Outcomes Nationwide in Heart Failure. Consensus recommendations for the management of chronic heart failure. *Am J Cardiol*. 1999;83:2A-38A.

5. Garg RG, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. *JAMA*. 1995;273:1450-1456.

6. Heidenrich PA, Lee TT, Massie BM. Effect of beta-blockade on mortality in patients with heart failure: a meta-analysis of randomized clinical trials. *J Am Coll Cardiol*. 1997;30:27-34.

7. Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. *N Engl J Med*. 1996;334:1349-1355.

8. Australia/New Zealand Heart Failure Research Collaborative Group. Randomized, placebo-controlled trial of carvedilol in patients with congestive heart failure due to ischaemic heart disease. *Lancet*. 1997;349:375-380.

9. CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS II). *Lancet*. 1999;353:9-13.

10. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomized Intervention Trial In Congestive Heart Failure (MERIT-HF). *Lancet*. 1999;353:2001-2007.

11. Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observations of each patient, I: introduction and design. *Br J Cancer*. 1976;34:585-612.

12. The International Steering Committee for the MERIT-HF Study Group. Rationale, design, and organisation of the metoprolol CR/XL randomized trial in heart failure (MERIT-HF). *Am J Cardiol*. 1997;80:54J-58J.

13. Rector TS, Cohn JN. Assessment of patient outcome with the Minnesota Living with Heart Failure questionnaire: reliability and validity during a randomized, double-blind, placebo-controlled trial of pimobendan. *Am Heart J*. 1992;124:1017-1025.

14. Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining the minimal important change in a disease-specific QoL questionnaire. *J Clin Epidemiol*. 1994;47:81-87.

15. Waagstein F, Wahlqvist I, Andersson B, et al. Metoprolol prevents left ventricular dilatation and increases exercise ejection fraction to the same extent in idiopathic and ischemic cardiomyopathy [abstract]. *Eur Heart J*. 1998;19(suppl):307.

16. Andersson B, Blomström-Lundqvist C, Hedner T, Waagstein F. Exercise hemodynamics and myocardial metabolism during long-term beta-adrenergic blockade in severe heart failure. *J Am Coll Cardiol*. 1991;18:1059-1066.

17. Waagstein F, Bristow MR, Swedberg K, et al. Beneficial effects of metoprolol in idiopathic dilated cardiomyopathy. *Lancet*. 1993;342:1441-1446.

18. The Metoprolol in Dilated Cardiomyopathy Trial Study Group. Three-year follow-up of patients randomized in the Metoprolol in Dilated Cardiomyopathy Trial. *Lancet*. 1998;351:1180-1181.

19. Fischer D, Stewart AL, Bloch DA, Lorig K, Laurent D, Holman H. Capturing the patient's view of change as a clinical outcome measure. *JAMA*. 1999; 282:1157-1162.

20. Colucci WS, Packer M, Bristow MR, et al. Carvedilol inhibits clinical progression in patients with mild symptoms of heart failure. *Circulation*. 1996;94:2800-2806.

21. Cohn JN, Fowler MB, Bristow MR, et al. Safety and efficacy of carvedilol in severe heart failure. *J Card Fail*. 1997;3:173-179.

22. Packer M, Colucci WS, Sackner-Bernstein JD, et al. Double-blind, placebo-controlled study of the effects of carvedilol in patients with moderate to severe heart failure: the PRECISE Trial. *Circulation*. 1996; 94:2793-2799.

23. Sandberg A, Ragnarsson G, Jonsson UE, Sjögren J. Design of a new multiple-unit controlled-release formulation of metoprolol—metoprolol CR/XL. *Eur J Clin Pharmacol*. 1988;33(suppl):S3-S7.

24. Andersson B, Åberg J. The effect on heart rate of immediate and slow-release metoprolol in patients with chronic heart failure [abstract]. *J Am Coll Cardiol*. 1999; 33:183A-184A.

25. Krum H, Whorlow S. Meta-analysis of effect of beta-blocker therapy on mortality in NYHA class IV CHF patients [abstract]. *Circulation*. 1999;100(suppl I):I203.